Form PTO-1390 (Rev. 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NO. H 3190 PCT/US

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 09/554386

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/07057	November 5, 1998	November 14, 1997

TITLE OF INVENTION

USE OF SELECTED PHYTOSTENOL ESTERS FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS

APPLICANT(S) FOR DO/EO/US

Bernd Fabry

Applicant herewith submits to the United States Designated/Elected Office (EO/DO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. □ This a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. □ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).

4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ■ A copy of the International Application as filed (35 U.S. C. 371(c)(2)).
   a. □ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. □ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ■ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. □ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. □ have been transmitted by the International Bureau.
   c. □ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.

8. □ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ■ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(UNEXECUTED)**

10. □ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. □ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. □ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ■ A FIRST preliminary amendment
    □ A SECOND or SUBSEQUENT preliminary amendment.

14. □ A substitute specification.

15. □ A change of power of attorney and/or address letter.

16. □ Other items or information.:

"Express Mail Post Office to Addressee" service Mailing Label Number EL541612054US .

422 Rec'd PCT/PTO 15 MAY 2000

U.S. Application No. (If known see CFR1.30)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/554386	PCT/EP98/07057	H 3190 PCT/US

17. ■ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

		CALCULATIONS	PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$840.00		
International preliminary examination fee paid to USPTO (37CFR 1.482)	$670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37CFR 1.445(a)(2))	$690.00		
Neither international preliminary examination fee (37CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$970.00		
International preliminary examination fee paid to USPTO (37CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96.00		

ENTER APPROPRIATE BASIC FEE AMOUNT			=	$ 840	00
Surcharge of **$130.00** for furnishing the oath or declaration later than □ 20 □ 30 months from the earliest claimed priority date 37 (CFR 1.492(e)).				$ 0	00
Claims	Number filed	Number Extra	Rate		
Total Claims	20 - 20 =	0	0 X $18.00	$ 0	00
Independent Claims	2 - 3 =	0	0 X $78.00	$ 0	00
Multiple dependent claims (s)(if applicable)		0	+ $260.00	$ 0	00
TOTAL OF ABOVE CALCULATIONS			=	$ 840	00
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 0	00
SUBTOTAL			=	$ 840	00
Processing fee of **$130.00** for furnishing the English translation later the □ 20 □ 30 months from the earliest claimed priority date (37CFR 1.492(f)).			+	$ 0	00
TOTAL NATIONAL FEE			=	$ 840	00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$ 0	00
TOTAL FEES ENCLOSED			=	$ 840	00
				Amount to be: refunded	$----------
				charged	$840.00

a. □ A check in the amount of $_____ to cover the above fees is enclosed.
b. ■ Please charge my Deposit Account No. 50-1177 in the amount of $840.00 to cover the above fees.
A triplicate copy of this sheet is enclosed. Order No. 00-0245 .
c. ■ The Assistant Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1177 . A triplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Cognis Corporation, Law Dept.
2500 Renaissance Blvd, Suite 200
Gulph Mills, PA 19406

SIGNATURE

Aaron R. Ettelman
NAME ATTORNEY FOR APPLICANT

42,516
REGISTRATION NUMBER

Form PTO 1390 (REV 5-93)

"Express Mail" mailing label number EL541612054US.

PATENT
Docket No. H 3190 PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE: PCT/EP98/07057
International Filing Date: November 5, 1998
Priority Date Claimed: November 14, 1997
Applicant: Bernd Fabry
Title: USE OF SELECTED PHYTOSTENOL ESTERS FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS
Applicants' Reference: H 3190 PCT/US

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box PCT
Washington, DC 20231

ATTN: DO/EO/US

Prior to the calculation of fees and examination of the above-identified national stage application pursuant to the accompanying submission under 35 U.S.C. §371, please amend the English translation of the International Application submitted herewith, without prejudice, as follows:

In the Specification:

Please amend the instant Specification, without prejudice, as follows:

At page 1, please delete all text above line 13, including the heading "Prior Art", and insert therefor the following:

--TITLE OF THE INVENTION

Hypocholesteremic Preparations Containing
Phytostenolesters of Conjugated Fatty Acids,
and Methods of Reducing Serum Cholesterol Levels Using the Same

BACKGROUND OF THE INVENTION--

At page 2, line 14 thereof, delete "Description of the Invention" and insert

therefor:

--BRIEF SUMMARY OF THE INVENTION

The present invention includes hypocholesteremic preparations comprising phytostenol esters of conjugated fatty acids, and methods of reducing serum cholesterol levels in mammals through administration of such preparations.--

At page 3, before line 1 thereof, insert:

--DETAILED DESCRIPTION OF THE INVENTION--

At page 7, line 34 thereof, delete "Commercial applicability".

Please add new page 11, which is attached hereto, containing an Abstract of the Disclosure, following the claims.

In the Claims:

Please add new claims 11-30, as follow:

--11. (New) A method of reducing serum cholesterol content in a mammal, said method comprising:

(i) providing a hypocholesteremic preparation comprising at least one phytostenol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms; and

(ii) administering the hypocholesteremic preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal.--

--12. (New) The method according to claim 11, wherein the at least one phytostenol ester comprises an ester of β-sitostenol or β-sitostanol.--

--13. (New) The method according to claim 11, wherein the conjugated fatty

acid is selected from the group consisting of conjugated linoleic acid and conjugated fish fatty acids.--

--14. (New) The method according to claim 11, wherein the conjugated fatty acid comprises conjugated linoleic acid.--

--15. (New) The method according to claim 11, wherein the at least one phytostenol ester comprises an ester of conjugated linoleic acid and β-sitostenol or β-sitostanol.--

--16. (New) The method according to claim 11, wherein the hypocholesteremic preparation further comprises a potentiating agent selected from the group consisting of tocopherols, chitosans, phytostenol sulfates, (deoxy)ribonucleic acids, and combinations thereof.--

--17. (New) The method according to claim 11, wherein the hypocholesteremic preparation further comprises a tocopherol.--

--18. (New) The method according to claim 11, wherein the hypocholesteremic preparation further comprises a chitosan selected from low-molecular weight chitosans and high-molecular weight chitosans.--

--19. (New) The method according to claim 11, wherein the hypocholesteremic preparation is encapsulated in gelatin, whereby a gelatin capsule is provided, prior to administering the preparation to the mammal.--

--20. (New) The method according to claim 18, wherein the at least one phytostenol ester is present in an amount of from about 0.1 to about 50% by weight, based on

the total weight of the gelatin capsule.--

--21. (New) A hypocholesteremic preparation comprising at least one phytostenol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms.--

--22. (New) The hypocholesteremic preparation according to claim 21, wherein the at least one phytostenol ester comprises an ester of β-sitostenol or β-sitostanol.--

--23. (New) The hypocholesteremic preparation according to claim 21, wherein the conjugated fatty acid is selected from the group consisting of conjugated linoleic acid and conjugated fish fatty acids.--

--24. (New) The hypocholesteremic preparation according to claim 21, wherein the conjugated fatty acid comprises conjugated linoleic acid.--

--25. (New) The hypocholesteremic preparation according to claim 21, wherein the at least one phytostenol ester comprises an ester of conjugated linoleic acid and β-sitostenol or β-sitostanol.--

--26. (New) The hypocholesteremic preparation according to claim 21, wherein the hypocholesteremic preparation further comprises a potentiating agent selected from the group consisting of tocopherols, chitosans, phytostenol sulfates, (deoxy)ribonucleic acids, and combinations thereof.--

--27. (New) The hypocholesteremic preparation according to claim 21, wherein the hypocholesteremic preparation further comprises a tocopherol.--

--28. (New) The hypocholesteremic preparation according to claim 21,

wherein the hypocholesteremic preparation further comprises a chitosan selected from low-molecular weight chitosans and high-molecular weight chitosans.--

--29. (New) The hypocholesteremic preparation according to claim 21, wherein the hypocholesteremic preparation is encapsulated in gelatin, whereby a gelatin capsule is provided.--

--30. (New) The method according to claim 28, wherein the at least one phytostenol ester is present in an amount of from about 0.1 to about 50% by weight, based on the total weight of the gelatin capsule.--

Please cancel claims 1-10, without prejudice.

REMARKS

Claims 11-30 are currently pending in the instant application.

The Specification has been amended to include the preferred section headings pursuant to 37 C.F.R. §1.77. An Abstract of the Disclosure has been added on a separate sheet following the claims. It is submitted that the amendments to the Specification made herein introduce no new matter. Their entry is therefore proper and respectfully requested.

Original claims 1-10 have been canceled and replaced with new claims 11-30 in order to remove multiple dependencies and to place the claims in more proper U.S. format for examination. New claims 11-30 are supported by the claims as originally filed and in the Specification, for example, at page 2, line 15, through page 4, line 6; at page 6, lines 2-7; at page 7, line 35, through page 8, line 29; and in the Examples. No new matter has been introduced. Entry is therefore proper and respectfully requested.

Preliminary Amendment of U.S. National Stage for International Application PCT/EP98/07057 filed November 5, 1998

Prompt examination of the instant application in view of the amendments made herein is respectfully requested.

Respectfully submitted,

BERND FABRY

May 15, 2000
(Date)

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ARE/ras

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USE OF SELECTED PHYTOSTENOL ESTERS FOR PRODUCING HYPOCHOLESTEREMIC PREPARATIONS

Field of the invention

The invention relates to the use of phytostenol esters, optionally together with selected potentiating agents, for producing preparations for decreasing the cholesterol content in the serum of warm-blooded animals.

Prior art

Hypocholesteremic active agents are understood as meaning preparations which lead to a decrease in the cholesterol content in the serum of warm-blooded animals without an inhibition or lowering of the formation of cholesterol in the blood occurring. Phytostenols, i.e. plant stenols, and their esters with fatty acids have already been proposed for this purpose by Peterson et al. in **J. Nutrit. 50, 191 (1953)**. The Patent Specifications **US 3,089,939, US 3,203,862** as well as the German Laid-Open Specification **DE-A 2035069** (Procter & Gamble) also point in the same direction. The active agents are customarily added to cooking or food oils and then ingested via the food, the amounts employed, however, as a rule being low and customarily below 0.5% by weight in order to prevent the food oils from becoming cloudy or the stenols from being precipitated on addition of water. For use in the foodstuffs area, in cosmetics, pharmaceutical preparations and in the agrarian sector, storage-stable emulsions of the stenol esters in sugar or polyglycerol esters are proposed in European Patent Application **EP-A1 0289636** (Ashai). The incorporation of sitostanol esters to decrease the blood cholesterol content in margarine, butter, mayonnaise, salad dressings and the like is proposed in European Patent Specification **EP-B1 0594612** (Raision).

The disadvantage, however, is that the phytostenol esters can customarily be added to the foodstuffs only in small amounts, as otherwise there is the danger that they will impair the taste and/or the consistency of the preparations. For a lasting effect on the cholesterol content in the blood, however, the intake of larger amounts of phytostenol esters would be desirable. Furthermore, the rate at which the substances decrease the content of cholesterol in the serum is worthy of improvement. The object of the invention consequently consisted in remedying these deficiencies.

Description of the invention

The invention provides the use of esters of phytostenols with fatty acids having 6 to 24 carbon atoms and at least two conjugated double bonds, optionally together with potentiating agents selected from the group consisting of tocopherols, chitosans, phytostenol sulfates and/or (deoxy)ribonucleic acids for producing hypocholesteremic preparations.

Surprisingly, it has been found that phytostenol esters based on conjugated fatty acids exhibit, with respect to reducing the cholesterol content in the blood, considerably higher activity than comparable phytostenol esters derived from saturated fatty acids, monounsaturated fatty acids or polyunsaturated fatty acids having two or more unconjugated double bonds. By combining the phytostenol esters to be used according to the invention (component a) with potentiating agents (component b) from the group of the chitosans, phytostenol sulfates and/or deoxy- or ribonucleic acids which for their part have little, if any, hypocholesteremic properties, it is possible to accelerate the reduction of the cholesterol content in the serum further. Moreover, encapsulated in gelatin, both the phytostenol esters and the mixtures of active agents can be taken orally without problems.

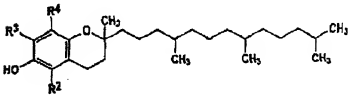
Phytostenol esters

Phytostenols (or synonymously phytosterols) are understood as meaning plant steroids which carry a hydroxyl group only on C-3, but otherwise no functional groups. As a rule, the phytostenols have 27 to 30 carbon atoms and a double bond in the 5/6, optionally 7/8, 8/9 or other positions. The unsaturated stenols can be hydrogenated to give the corresponding saturated stanols, which are likewise embraced by the present invention. Esterification of the stenols or stanols with unsaturated fatty acids having conjugated double bonds, preferably conjugated linoleic acid (CLA) or conjugated fish fatty acids, gives the substances forming the component (a). The phytostenol component of the esters can be derived from ergostenols, campestenols, stigmastenols, brassicastenols, preferably sitostenols or sitostanols and in particular β-sitostenols or β-sitostanols. The preparation can be carried out in a manner known per se, for example by direct esterification of the stenols with the fatty acids and subsequent hydrogenation of the esters, by direct esterification of the stanols with the fatty acids or, preferably, by transesterification and, if appropriate, hydrogenation of the stenols or stanols with the corresponding conjuene fatty acid methyl esters. A general preparation process by transesterification of the stenols/stanols with fatty acid lower alkyl esters or triglycerides in the presence of suitable catalysts, such as, for example, sodium ethylate or especially also enzymes is described in **EP-A2 0195311** (Yoshikawa). According to the invention, the fatty acid component of the phytostenol esters may also comprise minor amounts (less than 50 mol%) of saturated, monounsaturated or polyunsaturated non-conjugated proportions. Accordingly, for preparing the esters, it is possible to use, instead of pure conjugated linoleic acid, for example a technical-grade mixture having a high proportion of conjugated linoleic acid, commercially

available, for example, under the name Selin® CLA (Grünau). In the same manner, for preparing the phytostenol esters, it is also possible to transesterify the corresponding fatty acid methyl esters or triglycerides (for example Selin® CLA-TG) having a high conjuent content.

Tocopherols

Tocopherols which are suitable as potentiating agents for the phytostenol esters are understood as meaning chroman-6-ols (3,4-dihydro-2-*H*-1benzopyran-6-ols) substituted in the 2-position by 4,8,12-trimethyltridecyl radicals, which obey the formula (II)



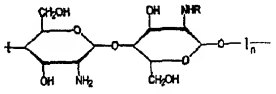
(II)

in which R^2, R^3 and R^4 independently of one another are hydrogen or a methyl group. Tocopherols belong to the bioquinones, i.e. polyprenylated 1,4-benzo- or naphthoquinones whose prenyl chains are saturated to a greater or lesser extent. Typical examples of tocopherols which are possible within the meaning of the invention as component (b1) are ubiquinones, boviquinones, K vitamins and/or menaquinones (2-methyl-1,4-naphthoquinones). In the case of the tocopherols, a differentiation is furthermore made between α, β, γ-, δ- and ε-tocopherols, where the latter can still have the original unsaturated prenyl side chain, and α-tocopherolquinone and -hydroquinone, in which the pyran ring system is opened. Preferably, as component (b), α-tocopherol (vitamin E) of the formula (II) is employed, in which R^2, R^3 and R^4 are methyl groups, or esters of α-tocopherol with carboxylic acids having 2 to 22 carbon atoms, such as,

for example, α-tocopherol acetate or α-tocopherol palmitate.

Chitosans

Chitosans, which are also suitable as potentiating agents (b2) for the phytostenol esters, are biopolymers and are included in the hydrocolloids group. Considered chemically, they are partially deacetylated chitins of different molecular weights, which contain the following - idealized - monomer unit (III)



(III)

In contrast to most hydrocolloids, which are negatively charged in the biological pH region, chitosans are cationic biopolymers under these conditions. The positively charged chitosans can interact with oppositely charged surfaces and are therefore employed in cosmetic hair- and body-care preparations and pharmaceutical preparations (cf. **Ullmann's Encyclopedia of Industrial Chemistry, 5th Ed., Vol. A6, Weinheim, Verlag Chemie, 1986, pp. 231-332**). Overviews on this subject have also appeared, for example, by B. Gesslein et al. in **HAPPI 27, 57 (1990)**, O. Skaugrud in **Drug Cosm. Ind. 148, 24 (1991)** and E. Onsoyen et al. in **Seifen-Öle-Fette-Wachse 117, 633 (1991)**. To produce chitosans, chitin, preferably the shell remains from crustaceans, which are available in large amounts as cheap raw materials, is used as a starting material. In a process which has been described for the first time by Hackmann et al., the chitin is customarily first deproteinated by addition of bases, demineralized by addition of mineral acids and finally deacetylated by addition of strong bases, it being possible for the

molecular weights to be distributed over a wide spectrum. Preference is given to using either low-molecular-weight chitosans having an average molecular weight of from about 50,000 to about 250,000 dalton or high-molecular-weight chitosans having an average molecular weight of from about 500,000 to about 2,000,000. Corresponding processes are known, for example, from **Makromol. Chem. 177, 3589 (1976)** or French Patent Application **FR-A 2701266**. Particular preference is given to using the types disclosed in the German patent applications **DE-A1 4442987** and **DE-A1 19537001** (Henkel), which have an average molecular weight of from 800,000 to 1,200,000 dalton, a viscosity according to Brookfield (1% by weight in glycolic acid) below 5000 mPas, a degree of deacetylation in the range from 80 to 88% and an ash content of less than 0.3% by weight. Suitable according to the invention are, in addition to the chitosans as typical cationic biopolymers, also anionic or nonionic derivatized chitosans, such as, for example, carboxylation, succinylation or alkoxylation products, as described, for example, in the German patent **DE-C2 3713099** (L'Oréal) and the German patent application **DE-A1 19604180** (Henkel).

Phytostenol sulfates

Phytostenol sulfates, which are also suitable as potentiating agents (b3) for the phytostenol esters, are known substances which can be prepared, for example, by sulfation of phytostenols with a complex of sulfur trioxide and pyridine in benzene [cf. **J. Am. Chem. Soc. 63, 1259 (1941)**]. Typical examples are the sulfates of ergostenols, campestenols, stigmastenols and sitostenols. The phytostenol sulfates can be present as alkali metal and/or alkaline earth metal salts, as ammonium, alkylammonium, alkanolammonium and/or glucammonium salts. As a rule, they are employed in the form of their sodium salts.

(Deoxy)ribonucleic acids

(Deoxy)ribonucleic acids (DNA or RNA), which are suitable as the last group of potentiating agents (b4) for the phytostenol esters, are understood as meaning high molecular weight, threadlike polynucleotides which are derived from 2'-deoxy-β-D-ribonucleosides or D-ribonucleosides, which for their part in turn are synthesized from equivalent amounts of a nucleobase and the pentose 2-deoxy-D-ribofuranose or D-ribofuranose. As nucleobases, the DNA or RNA can contain the purine derivatives adenine and guanine and also the pyrimidines cytosine and thymine or uracil. In the nucleic acids, the nucleobases are linked N-glycosidically with carbon atom 1 of the ribose, adenosines, guanosines, cytidines and thymidines being formed in the individual case. In the acids, a phosphate group links the 5'-hydroxyl group of the nucleosides with the 3'-OH group of the following nucleoside in each case by means of a phosphodiester bridge with formation of single-stranded DNA or RNA. Because of the large ratio of length to diameter, DNA and RNA molecules are prone, even on mechanical stress, for example during extraction, to strand breakage. For this reason, the molecular weight of the nucleic acids can reach 10^3 to 10^9 daltons. Within the meaning of the invention, concentrated DNA and RNA solutions are employed, which are distinguished by a liquid-crystalline behavior. Preferably, deoxy- and ribonucleic acids are employed which are obtained from marine sources, for example by extraction of fish sperm, and which have a molecular weight in the region from 40,000 to 1,000,000 daltons.

Commercial applicability

The mixtures of active agents of the invention can contain the phytostenol esters (a) and the potentiating agents (b) in a ratio by weight of from 99:1 to 1:99, preferably from 90:10 to 10:90, in particular from 70:25 to 25:75 and particularly

preferably from 60:40 to 40:60, where the only thing that has to be made sure is that, with the use according to the invention, an amount of the component (a) which is sufficient for lowering the cholesterol content in the blood is administered. In a special embodiment of the invention, the phytostenol esters - on their own or together with the potentiating agents - are encapsulated in a manner known per se in gelatin, the components (a) and, if appropriate, (b) being in each case employed in amounts of from 0.1 to 50, preferably from 1 to 30, in particular from 5 to 25 and particularly preferably from 10 to 15% by weight, based on the weight of the gelatin capsules. A further aspect of the invention relates to the finding that the encapsulation of the phytostenol esters in gelatin is an advantageous embodiment for oral administration of the active agents.

A further administration form of the phytostenol esters are suppositories which can be introduced rectally or vaginally and which may, as suppository base, likewise comprise gelatin, if appropriate in combination with glycerol, or else synthetic fats and/or waxes, polyethylene glycols or natural components, such as, for example, cocoa butter. In addition, it is possible to dissolve or disperse the phytostenol esters in customary foodstuffs, such as, for example: salad oils, dressings, mayonnaises, margarines, butter, deep-frying fats, cocoa products, sausage and the like.

Examples

Examples 1 to 5, Comparative Examples C1 to C5

Gelatin capsules (weight about 1.5 g) having a content of 5% by weight of various β-sitostenol esters and, if appropriate Vitamin E and also 0.5% by weight of radiolabeled cholesterol were prepared. To investigate the hypocholesteremic action, male rats (individual weight about 200 g) were allowed to fast

overnight. The following day, a comminuted gelatin capsule was introduced into the experimental animals in each case with some salt-containing water by means of a stomach tube. After 3, 6, 12, 24 and 48 h, blood was taken from the animals and the content of radioactive cholesterol was determined. The results, which represent the mean value of the measurements of 10 experimental animals, are summarized in Table 1. The details on the decrease in the radioactivity are in each case interpreted with respect to a blind group of experimental animals, to which only gelatin capsules having a content of 20% by weight of vitamin E and an appropriate amount of radiolabeled cholesterol had been administered. The mixtures 1 to 5 are according to the invention; the mixtures C1 to C3 serve for comparison.

Table 1

Hypocholesteremic action (quantitative data as % by weight based on gelatin capsule)

Composition/activity	1	2	3	4	5	C1	C2	C3
Conjuene fatty acid β-sitostenol ester*	5	–	–	–	–	–	–	–
Conj. C_{12}-C_{24}-fish fatty acid β-sitostenol ester	–	5	–	–	–	–	–	–
Conjuene fatty acid β-sitostanol ester*	–	–	5	–	–	–	–	–
Conj. C_{12}-C_{24}-fish fatty acid β-sitostenol ester	–	–	–	5	5	–	–	–
Lauric acid β-sitostanol ester	–	–	–	–	–	–	–	–
Oleic acid β-sitostanol ester	–	–	–	–	–	5	–	–
Linoleic acid β-sitostanol ester	–	–	–	–	–	–	5	–
Vitamin E	–	–	–	–	5	–	–	5
Radioactivity [%-rel]								
- after 3 h	95	95	95	95	95	95	95	95
- after 6 h	80	79	78	78	75	84	82	83
- after 12 h	72	70	68	67	61	76	74	73
- after 24 h	45	45	43	43	39	51	48	47
- after 48 h	21	20	18	17	15	30	26	25

*) fatty acid base: Selin® CLA (Grünau/Illertissen)

Patent Claims

1. The use of esters of phytostenols with fatty acids having 6 to 24 carbon atoms and at least 2 conjugated double bonds for producing hypocholesteremic preparations.

2. The use as claimed in claim 1, **wherein** esters of β-sitostenol or β-sitostanol are employed.

3. The use as claimed in claims 1 and 2, **wherein** esters of β-sitostenol and/or β-sitostanol with conjugated linoleic acid are employed.

4. The use as claimed in claims 1 and 2, **wherein** esters of β-sitostenol and/or β-sitostanol with conjugated fish fatty acid are employed.

5. The use as claimed in claims 1 to 4, **wherein** the phytostenol esters are employed together with potentiating agents selected from the group consisting of tocopherols, chitosans, phytostenol esters and (deoxy)ribonucleic acids and mixtures thereof.

6. The use as claimed in claims 1 to 5, **wherein** the potentiating agent employed is vitamin E.

7. The use as claimed in claims 1 to 6, **wherein** the potentiating agents employed are chitosans having an average molecular weight in the range from 50,000 to 250,000 and/or 500,000 to 2,000,000 dalton.

8. The use as claimed in claims 1 to 7, **wherein** the potentiating agents) employed are marine deoxyribonucleic acids, having a molecular weight in the range from 40,000 to 1,000,000 dalton.

9. The use as claimed in claims 1 to 8, **wherein** components (a) and, if appropriate, (b) are encapsulated in gelatin.

10. The use as claimed in claim 9, **wherein** the phytostenol esters are employed in amounts from 0.1 to 50% by weight - based on the weight of the gelatin capsules.

ABSTRACT OF THE DISCLOSURE

A hypocholesteremic preparation containing at least one phytostenol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms is disclosed. Methods of reducing serum cholesterol content in a mammal via administration of hypocholesteremic preparations described herein are also disclosed.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing

Attorney Docket Number	H 3190 PCT/US
First Named Inventor	FABRY, Bernd
COMPLETE IF KNOWN	
Application Number	09/554,386
Filing Date	07/19/2000
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:
My residence, post office address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF SELECTED PHYTOSTENOL ESTERS FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 11/05/1998 as United States Application Number or PCT International Application Number PCT/EP98/07057 and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1 56

I hereby claim foreign priority benefits under Title 35, United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
197 50 422.1	Germany	11/14/1997	☐	☐	☒

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

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DECLARATION

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U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
	PCT/EP98/07057	11/05/1998	

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As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: [ ] A petition has been filed for this unsigned

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